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EXAMINER	
KAM, CHIH MIN	

ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 10/04/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/750,022	ISAACS, INDU J.	
	Examiner	Art Unit	
	Chih-Min Kam	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 September 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-54 and 58-78* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *31-42* is/are allowed.

6)☒ Claim(s) *1-8,10-22,43-46,49-55,58,59,63-71 and 73-78* is/are rejected.

7)☒ Claim(s) *9,23-30,47,48 and 72* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. *0704*.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. The finality of the previous Office Action dated June 8, 2004 is withdrawn due to a new ground rejection.

Status of the Claims

2. Claims 1-54 and 58-78 are pending.

Applicants' amendment filed September 07, 2004 is acknowledged. Applicants' response has been fully considered. Claims 25-29, 42, 49 and 59 have been amended, claims 56 and 57 have been cancelled, and new claims 77 and 78 have been added. Therefore, claims 1-54 and 58-78 are examined.

Objection Withdrawn

3. The previous objection of claims 56, 57 and 59 is withdrawn in view of applicants' cancellation of the claim, applicants' amendment to the claim, and applicants' response at pages 13-14 in the amendment filed September 07, 2004.

Rejection Withdrawn

Claim Rejections - 35 USC § 112

4. The previous rejection of claims 2-4, 23-30, 34, 35, 37, 38, 41, 42, 44, 45, 47-54, 56, 57, 63, 65-67 are rejected under 35 U.S.C. 112, second paragraph under 35 U.S.C. 112, second paragraph, as being indefinite, is withdrawn in view of applicants' cancellation of the claim, applicants' amendment to the claim, and applicants' response at pages 14-17 in the amendment filed September 07, 2004.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 17 and 58-63 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

6. Claims 17 and 58, 60-63 are indefinite because of the use of the term "one or more substitutions, additions, deletions, or modifications". The cited term renders the claim indefinite, it is not clear where the substitutions, additions, deletions, or modifications occur in the sequence and how many amino acids are substituted, added, deleted or modified, and what resulting sequence is.

7. Claim 59 is indefinite as to the claim recites amino acid substitutions at various positions without indicating "SEQ ID NO:" of the reference sequence, it is not clear what amino acid sequence these positions are referring to.

In response, applicants indicate the amino acid sequence of GLP-2 was well known in the art prior to the earlier priority date of the application, and further cite many patents and references to indicate various vertebrate forms of GLP-2 include, for example, rat GLP-2 and its homologues including ox GLP-2, porcine GLP-2, degu GLP-2, bovine GLP-2, guinea pig GLP-2, hamster GLP-2, human GLP-2, rainbow trout GLP-2, and chicken GLP-2, the sequences of which have been reported by many authors, and the practice of those skilled in the art was to indicate amino acid substitutions in the GLP-2 sequence by reciting, for example, "Lys^{20}GLP-2" where the amino acid substitution, followed by the position number in superscript, precedes the peptide indicator GLP-2. The disclosure of the instant application conforms to this practice and

describes GLP-2 as a 33 amino acid peptide (See e.g., page 6, lines 16-18 of the specification; pages 17-19 of the response).

The response has been considered, however, the argument is not found persuasive because there are sequence variations among different naturally occurring vertebrate GLP-2 peptides (see Fig. 2 of Buhl et al., J. Biol. Chem. 263, 8621-8624 (1988)) and synthetic GLP-2 peptides (e.g., $Lys^{20}Arg^{30}$GLP-2(1-33), $Arg^{30}Lys^{34}$GLP-2(1-35) in WO 99/43361, the reference has shown the parent sequence at page7), thus, it is not clear which amino acid sequence is used for the substitution, and what resulting sequence the GLP-2 analog has, if only the position of substitution and amino acid residue substituted are given without a reference sequence. Furthermore, it is noted that both U. S. Patents 5,789,379 and 5,834,428 have "SEQ ID NO:" cited in the claims when there is a variation indicated in the sequence.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claims 1-8, 10, 22, 49-55, 58, 63-71, 73 and 78 are rejected under 35 U.S.C. 103(a) as being unpatentable over Knudsen *et al.* (WO 99/43361) in view of Kornfelt *et al.* (U. S. Patent 5,652,216, July 29, 1997).

Knudsen *et al.* teach a pharmaceutical composition comprising a GLP-2 derivative or analog, an isotonic agent such as mannitol, a buffer of histidine or sodium phosphate, a pharmaceutical acceptable carrier, a preservative and a surfactant, where the solubility and

stability of GLP-2 is improved and the pharmaceutical formulation has pH 6.9 if phosphate buffer is used (page 4, line 19-29; page 3, lines 24-25; claims 2-4 and 10). The reference also indicates the concentration of the GLP-2 derivative is more than 0.5 mg and less than 100 mg/ml (page 4, lines 9-12; page 13, lines 16-19; claims 5-8), the formulation can be obtained in lyophilized form (page 13, line 10; claim 22), GLP-2 derivative has an amino acid sequence of HGDGSFSDEMNTILDNLAARDFINWLIQTKITD (having the same sequence as h(Gly2)GLP-2) or its variants at several positions (page 7, lines 1-12; claims 58, 63-71, 73), and the pharmaceutical composition can be administered by injection or means of infusion pump to treat small bowl syndrome or intestinal inflammation (page 12, lines 13-16; page 13, 16-24, claims 49-54 and 78). However, Knudsen *et al.* do not disclose using histidine as a stabilizing agent. Kornfelt *et al.* disclose using stabilizing amount of a pharmaceutically acceptable ampholyte such as glycine, histidine (5, 10 or 20 mM corresponding about 1.7, 3.4 or 6.8%) or GlyGly in a pharmaceutical preparation comprising glucagon (column 2, lines 21-45; Table 1; claims 1 and 55). At the time the invention was made, it would have been obvious that a person of ordinary skill in the art is motivated to prepare a pharmaceutical composition of GLP-2 as indicated by Knudsen *et al.* with the addition of histidine as a stabilizing agent as taught by Kornfelt *et al.* because stabilizing amount of histidine has been shown to stabilize glucagon in the formulation (Table 1; Fig. 1; >90% glucagons detected after 4 weeks at 60 °C), and GLP-2 is a glucagons like peptide. Thus, the combined references result in the claimed invention and was, as a whole, prima facie obvious at the time the claimed invention was made.

9. Claims 11, 12, 74 and 75 are rejected under 35 U.S.C. 103(a) as being unpatentable over Knudsen *et al.* in view of Kornfelt *et al.* as applied to claims 1-8 and 10 above, further in view of Hora *et al.* (U. S. Patent 5,997,856).

The combined references of Knudsen *et al.* and Kornfelt *et al.* teach a pharmaceutical composition comprising a GLP-2 derivative or analog, an isotonic agent such as mannitol, a buffer of sodium phosphate, a stabilizing agent of histidine, a pharmaceutical acceptable carrier, a preservative and a surfactant as shown in the section above (see paragraph 8). However, Knudsen *et al.* and Kornfelt *et al.* do not disclose the concentration of mannitol in the pharmaceutical composition. Hora *et al.* disclose 1-5% mannitol is used as a bulking agent in a protein preparation (column 25, lines 7-14). At the time the invention was made, it would have been obvious that a person of ordinary skill in the art is motivated to prepare a pharmaceutical formulation of GLP-2 analogs as indicated by Knudsen *et al.* and Kornfelt *et al.* with a known concentration of mannitol taught by Hora *et al.* (claims 11, 12, 74 and 75) to treat a gastrointestinal disease because the addition of a known concentration of mannitol can further improve the stability of the pharmaceutical composition. Thus, the combined references result in the claimed invention and was, as a whole, prima facie obvious at the time the claimed invention was made.

10. Claims 13-15, 17-20 and 76 are rejected under 35 U.S.C. 103(a) as being unpatentable over Knudsen *et al.* in view of Kornfelt *et al.* as applied to claims 1-8 and 10 above, further in view of Drucker *et al.* (WO 97/39031).

The combined references of Knudsen *et al.* and Kornfelt *et al.* teach a pharmaceutical composition comprising a GLP-2 derivative or analog, an isotonic agent such as mannitol, a

buffer of sodium phosphate, a stabilizing agent of histidine, a pharmaceutical acceptable carrier, a preservative and a surfactant as shown in the section above (see paragraph 8). However, Knudsen *et al.* and Kornfelt *et al.* do not disclose the source of GLP-2 and DPP-IV-resistant GLP-2 analogs. Drucker *et al.* disclose the sequence of human GLP-2, h[Gly2]GLP-2 analog, and DPP-IV-resistant GLP-2 analogs, where the Ala at position 2 has been modified (page 7, lines 8-20; page 9, lines 11-22, Table 1). At the time the invention was made, it would have been obvious that a person of ordinary skill in the art is motivated to prepare the pharmaceutical composition as indicated by Knudsen *et al.* and Kornfelt *et al.* using the GLP-2 analogs taught by Drucker *et al.* (claims 13-15, 17-20 and 76) to treat a gastrointestinal disease because the use of DPP-IV resistant GLP-2 analogs in the pharmaceutical composition would result in a more stable pharmaceutical composition in vivo, where the GLP-2 analogs are degraded more slowly in vivo condition. Thus, the combined references result in the claimed invention and was, as a whole, prima facie obvious at the time the claimed invention was made.

11. Claims 16 and 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Knudsen *et al.* in view of Kornfelt *et al.* as applied to claims 1-8 and 10 above, further in view of Thim *et al.* (U.S. Patent 5,912,229).

The combined references of Knudsen *et al.* and Kornfelt *et al.* teach a pharmaceutical composition comprising a GLP-2 derivative or analog, an isotonic agent such as mannitol, a buffer of sodium phosphate, a stabilizing agent of histidine, a pharmaceutical acceptable carrier, a preservative and a surfactant as shown in the section above (see paragraph 8). However, Knudsen *et al.* and Kornfelt *et al.* do not disclose the use of GLP-2 receptor to identify peptides that bind GLP-2 receptor or as GLP-2 receptor antagonist. Thim *et al.* disclose a GLP-2 receptor

is identified and cloned, and a cell line stably expressing the receptor is used in a screening assay to identify the antagonist of GLP-2 receptor (column 10, lines 43-59). At the time the invention was made, it would have been obvious that a person of ordinary skill in the art is motivated to prepare the pharmaceutical composition as indicated by Knudsen *et al.* and Kornfelt *et al.* (claims 16 and 21) using the GLP-2 analogs taught by Thim *et al.* to treat a GLP-2 receptor-associated disease because the pharmaceutical composition containing the GLP-2 receptor antagonist is stabilized and useful in the treatment of GLP-2 receptor-associated diseases. Thus, the combined references result in the claimed invention and was, as a whole, prima facie obvious at the time the claimed invention was made.

12. Claims 43-46 and 77 are rejected under 35 U.S.C. 103(a) as being unpatentable over Knudsen *et al.* in view of Kornfelt *et al.* as applied to claims 1-8 and 10 above, further in view of Drucker (U. S. Patent 5,952,301).

The combined references of Knudsen *et al.* and Kornfelt *et al.* teach a pharmaceutical composition comprising a GLP-2 derivative or analog, an isotonic agent such as mannitol, a buffer of sodium phosphate, a stabilizing agent of histidine, a pharmaceutical acceptable carrier, a preservative and a surfactant as shown in the section above (see paragraph 8). However, Knudsen *et al.* and Kornfelt *et al.* do not disclose a kit comprising a lyophilized GLP-2 formulation. Drucker disclose a kit comprising GLP-2 or GLP-2 analogs (column 2, lines 56-61). At the time the invention was made, it would have been obvious that a person of ordinary skill in the art is motivated to prepare a kit as taught by Drucker (claims 43-46 and 77) using the pharmaceutical composition as indicated by Knudsen *et al.* and Kornfelt *et al.* to treat a gastrointestinal disease because the kit containing the stabilized pharmaceutical composition is

useful in the treatment of a gastrointestinal disease. Thus, the combined references result in the claimed invention and was, as a whole, prima facie obvious at the time the claimed invention was made.

13. Claims 9, 23-30, 47, 48 and 72 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

14. Claims 1-8, 10-22, 43-46, 49-55, 58, 59, 63-71 and 73-78 are rejected, and claims 9, 23-30, 47, 48 and 72 are objected to. It appears that claims 31-42 are free of prior art and allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chih-Min Kam whose telephone number is (571) 272-0948. The examiner can normally be reached on 8.00-4:30, Mon-Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber can be reached at 571-272-0925. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Chih-Min Kam, Ph. D. CMK
Patent Examiner

CMK
September 25, 2004

JON WEBER
SUPERVISORY PATENT EXAMINER